Spinal and Bulbar Muscular Atrophy

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KEYWORDS

• Spinal and bulbar muscular atrophy • Kennedy disease • Motor neuron disease
• Androgen receptor

KEY POINTS

- Spinal and bulbar muscular atrophy is a neuromuscular disorder with degeneration of lower motor neurons and muscle resulting in slowly progressive weakness, atrophy, and fasciculations.
- Genetic testing of a CAG trinucleotide repeat in the androgen receptor gene confirms the diagnosis. Laboratory testing of serum creatine kinase and electrophysiology studies are frequently abnormal, and testing of swallow function may help in identifying those at risk of developing aspiration.
- There is currently no effective therapy to prevent progression of the disease, and management is focused on preventing complications and improving mobility and function.

INTRODUCTION

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy disease,[1] is caused by progressive degeneration of the lower motor neurons and muscle. A trinucleotide (CAG) repeat expansion in the androgen receptor (AR) gene on the X chromosome is the cause.[2] Repeat lengths of 38 to 68 CAGs have been reported in patients, with 11 to 32 CAGs in normal individuals.[3–5] Affected men typically develop symptoms and findings in the limb and bulbar muscles with weakness, atrophy, and fasciculations. Bulbar weakness indicates NP8/MP7 overlap.[6] The age of onset correlates inversely with the length of the CAG repeat,[7] with earlier age of onset in those with longer repeats. The disease has been widely reported in European, Asian, and American populations.

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MECHANISM

The CAG repeat is expressed as an expanded polyglutamine tract in the AR, and studies in animal models and patients indicate that androgen-dependent gain of function by the receptor results in toxicity of the mutant protein.[8,9] Unlike other polyglutamine diseases in which the native function of the disease protein is unclear, the function of the AR has been well characterized. In the absence of androgen, the receptor is localized in the cytoplasm and bound to heat shock proteins. Testosterone or dihydrotestosterone binding by the receptor results in nuclear translocation and binding to androgen-responsive elements throughout the genome.[10] Translocation of the mutant AR into the nucleus also seems to be necessary for toxicity, as deletion of the nuclear localization signal prevents toxicity in a mouse model.[11] The features of disease result from a loss as well as gain in function of the receptor because patients often have gynecomastia and reduced fertility in addition to weakness and muscle atrophy. The mutated receptor has a propensity to aggregate and form inclusions in tissues where it is expressed.[12] Toxicity of the mutant AR is likely mediated through transcriptional dysregulation,[13] with disruption of mitochondrial function,[14] protein homeostasis,[15] and cellular signaling.[16] The transcriptional coactivator CREB-binding protein (CBP) is sequestered and depleted in SBMA and other polyglutamine diseases.[17] Defects in autophagy, the cellular process responsible for degrading and recycling cellular constituents, have been implicated in the disease.[18] Alteration of autophagy through genetic and pharmacologic mechanisms has been shown to be protective in several models of the disease.[11]

Although the AR is expressed in various tissues throughout the body, the predominant site of toxicity is in the spinal cord and muscles. Brain stem motor nuclei are also susceptible, except for the third, fourth, and sixth cranial nerves. Loss of anterior horn cells in the spinal cord has been described,[19] and a direct role of the mutant AR in muscle degeneration has been demonstrated in animal models of the disease.[20] Several studies have reported that selective expression or correction of the mutant AR in mouse muscle can reproduce or ameliorate the disease manifestations, respectively.[21,22] The relative contributions of the motor neuron and muscle toward the pathogenesis in patients remain to be defined. Affected males can also experience mild sensory loss in the distal extremities from degeneration of dorsal root ganglion cells.

DISEASE COURSE

The average age of onset is usually in the mid 40s, with a range of 18 to 64 years of age.[4] Clinical features of the disease can vary among affected individuals in the same family. Weakness affects the upper and lower extremities, following NP7 with both proximal and distal muscles.[6] Features of androgen insensitivity, such as sexual dysfunction, gynecomastia, and testicular atrophy, may be apparent before motor involvement. Overall, the most common presenting features are weakness, tremor, and cramping.[3,4] The progression of weakness in the disease is slow, with an approximately 2% decrease in muscle strength by quantitative muscle testing (QMT) per year.[23] Patients may experience a stepwise decrease in performance as critical thresholds needed for function tend to be more readily perceived as function is lost. Patients with SBMA generally have good preservation of mobility until late in the disease, requiring a cane or other assistive device at a median age of 60 years. Those with progressive loss of gait and balance function may eventually require a wheelchair. Bulbar manifestations, including dysarthria and nasal speech, can present early in the disease course and may progress to dysphagia. There are subtle to prominent tongue and facial muscle fasciculations, whereas limb fasciculations are not prominent.

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